J. Pharm. Pharmacol. 1980, 32: 39–44 Received May 17, 1979

Stereoselective actions of substituted benzamide drugs on cerebral dopamine mechanisms

P. JENNER, A. CLOW, C. REAVILL, A. THEODOROU AND C. D. MARSDEN*

University Department of Neurology, Institute of Psychiatry & King's College Hospital Medical School, Denmark Hill, London, SE5 U.K.

Apomorphine-induced locomotor activity in reserpine-pretreated mice was antagonized by pretreatment with (−)-sulpiride and (−)-sultopride. The (+)-enantiomers were inactive. Apomorphine- and amphetamine-induced stereotyped behaviour in rats were antagonized by (−)-sultopride but not by the (+)-enantiomer. Neither enantiomer of sulpiride prevented the onset of the stereotyped response. Both (−)-sulpiride and (−)-sultopride induced increases in striatal and mesolimbic HVA and DOPAC concentrations; (+)-sultopride elevated striatal and mesolimbic DOPAC concentrations but not HVA, while (+)-sulpiride had no effect on HVA or DOPAC in either area. Dopamine concentrations were reduced by the enantiomers of sultopride but not by sulpiride. Low concentrations (10^{-9} – 10^{-6} M) of the (−)-enantiomers of both drugs displaced [^{3}H]spiperone from its specific binding site in rat striatal preparations, but the (+)-enantiomers were 40 and 100 times less active. However, neither enantiomer of either drug anatagonized the dopamine-induced stimulation of adenylate cyclase in rat striatal preparations. The data suggest that the central pharmacological activity of sulpiride and sultopride resides in the (−)-enantiomers and that this activity occurs at cerebral dopamine receptors not dependent on adenylate cyclase for functional activity.

Substituted benzamide drugs such as sulpiride and metoclopramide are cerebral dopamine antagonists that exhibit two major differences from typical dopamine receptor antagonists; they do not produce marked catalepsy (Costall & Naylor 1975; Elliott et al 1977) and do not antagonize dopamine stimulation of adenylate cyclase in striatal tissue (Trabucchi et al 1975; Jenner et al 1978 a,b). These differences suggest that such drugs are selective antagonists at a sub-class of cerebral dopamine receptors not dependent on adenylate cyclase for the continuation of neuronal transmission. A selective effect of drugs on a neuronal pathway is often indicated by a stereoselectivity of action. For example, *cis*- and *trans*-flupenthixol or (+)- and (−)-butaclamol exhibit markedly different potencies in their actions on cerebral dopamine receptors (Burt et al 1976; Iversen et al 1976).

Those substituted benzamide drugs containing a pyrrolidine ring are optically active. Thus, the enantiomers of sulpiride and sultopride are separated by their geometry at the C-1 atom of the pyrrolidine ring. We have tested the activity of the enantiomers of these compounds on a number of in vivo and in vitro models associated with cerebral dopamine function.

* Correspondence.

MATERIALS AND METHODS

The enantiomeric benzamides (+)- or (−)-sulpiride (*N*-[1′-ethyl-2′-pyrrolidinylmethyl]-2-methoxy-5-sulphamoylbenzamide) and (+)- or (−)-sultopride (*N*-[1′-ethyl-2′-pyrrolidinylmethyl]-2-methoxy-5-ethylsulphonylbenzamide) were supplied by SESIF (France).

Locomotor activity

Locomotor activity was measured in Animex activity meters (LKB Farad Ltd.). Male Swiss S or P strain mice (20–25 g; Animal Suppliers Ltd.) were pretreated with reserpine (10 mg kg^{-1} i.p.; Halewood Chemicals) 12–24 h before activity measurement. Animals received either saline (0·1 ml 0·9% NaCl) or the enantiomers of sultopride (2·5–40 mg kg^{-1} i.p.) or sulpiride (4–64 mg kg^{-1} i.p.) 1 h before the administration of apomorphine hydrochloride (2 mg kg^{-1} i.p.; Evans Medical). Activity was recorded in the subsequent 2 h for at least 6 batches of 3 animals at each dose level. Results are expressed as mean Animex counts during the 2 h following apomorphine administration (±1 s.e.m.).

Stereotyped behaviour

Stereotyped behaviour was assessed in male Wistar rats (150–200 g; Animal Suppliers Ltd.) following the administration of apomorphine hydrochloride (0·5 mg kg^{-1} s.c. 15 min previously) or (+)-amphet-

amine sulphate (5 mg kg^{-1} i.p. 30 min previously) according to the scale: 0 = normal, 1 = continuous locomotor activity, discontinuous sniffing, 2 = discontinuous locomotor activity, continuous sniffing, 3 = discontinuous biting, licking and gnawing, 4 = continuous biting, licking or gnawing. Animals were pretreated with the enantiomers of sulpiride or sultopride (4–128 mg kg^{-1} i.p.) or saline (0·1 ml) 1 h before apomorphine or amphetamine administration. Results are expressed as the mean stereotypy score for at least 8 rats at each dose level (±1 s.e.m.).

Striatal and mesolimbic dopamine, HVA and DOPAC concentrations

Striatal and mesolimbic dopamine, homovanillic acid (HVA) and 3,4-dihydroxyphenylacetic acid (DOPAC) concentrations were determined in neostriatal and mesolimbic (nucleus accumbens and tuberculum olfactorium) areas of brain by Sephadex G_{10} column separation and subsequent fluorimetric analysis according to Westerink & Korf (1977). Male Wistar rats (150–200 g) received the enantiomers of sulpiride (2–100 mg kg^{-1} i.p.) 3 h and sultopride (2–50 mg kg^{-1} i.p.) 1·5 h before death. The time of pretreatment was chosen on the basis of the maximal elevation of HVA and DOPAC produced by the racemate of each drug (Elliott et al 1977; unpublished data). Animals were killed by cervical dislocation and decapitation, the brain rapidly removed onto ice and the dopamine containing areas dissected out and frozen at −20 °C. Analysis was completed within 24 h of sample removal.

Striatal dopamine-sensitive adenylate cyclase

Dopamine-sensitive adenylate cyclase in the striatum from male Wistar rats (150–200 g) was measured using the method of Miller et al (1974). Dopamine (10^{-4} M) was used to stimulate adenylate cyclase activity. The enantiomers of sulpiride and sultopride were incorporated into the system in concentrations of 10^{-8}–10^{-4} M (as the base).

Specific [^{3}H]spiperone binding to striatal preparations

Neuroleptic receptor binding was assayed in striatal preparations from female Wistar rats (150–200 g) by the technique of Leysen et al (1978a). [^{3}H]Spiperone (26 Ci $mmol^{-1}$; Radiochemical Centre) 0·5 nM was used to label the striatal preparations. The enantiomers of sulpiride and sultopride (or vehicle) were incorporated into the system at concentrations of 10^{-10} – 5×10^{-6} M. Incubates containing either (+)- or (−)-butaclamol hydrochloride (Ayerst Laboratories Ltd.) (2×10^{-6} and 2×10^{-7} M respectively) were also included to distinguish specific from non-specific [^{3}H]spiperone binding.

Statistical analysis

Stereotypy data were analysed using the Mann-Whitney U test for non-parametric data. All other results were analysed using Student's *t*-test for grouped data.

RESULTS

Locomotor activity

Apomorphine hydrochloride (2 mg kg^{-1} i.p.) restored locomotion in reserpinized mice (Table 1). The prior administration of (−)-sulpiride (4–64 mg kg^{-1} i.p.) or (−)-sultopride (2·5–40 mg kg^{-1} i.p.) antagonized the apomorphine-induced locomotor response. However, neither drug completely prevented the response to apomorphine in the doses used and the small reduction observed was not dose dependent. Administration of (+)-sulpiride (4–64 mg kg^{-1} i.p.) or (+)-sultopride (2·5–40 mg kg^{-1} i.p.) had no effect on apomorphine reversal of prior reserpinization.

Table 1. The effect of (+)- or (—)-sulpiride or sultopride on apomorphine (2 mg kg^{-1} i.p.)-induced locomotor activity in reserpine (10 mg kg^{-1}; 18–24 h previously) pretreated mice as judged using Animex activity meters. Control animals produced 7298 ± 220 (n = 50) Animex counts in the 2 h period after apomorphine administration compared with 234 ± 25 (n = 49) in the 1 h before apomorphine. Each value for drug-treated animals is the mean (± s.e.m.) for at least 6 determinations. Each dosage group was run in parallel with a control group of animals and the results are expressed as a percentage of activity in the interdigitated control experiments. The control percentages shown represent the mean control values (±s.e.m.) obtained for both enantiomers of each drug at all dosage levels used.

Drug and dose (mg kg^{-1})	Animex counts in 2 h after apomorphine (2 mg kg^{-1} i.p.) as % control values (+)-enantiomer	(—)-enantiomer
Sulpiride		
0	100·0 ± 4·0	
4	93·2 ± 7·8	80·2 ± 5·9*
8	87·8 ± 7·8	75·8 ± 4·1*
16	96·4 ± 10·6	70·1 ± 6·6*
32	85·2 ± 6·1	67·9 ± 7·4*
64	103·0 ± 10·6	68·8 ± 4·3*
Sultopride		
0	100·0 ± 7·6	
2·5	96·3 ± 5·3	74·3 ± 3·9*
5·0	85·5 ± 3·7	74·0 ± 8·0*
10	90·1 ± 8·0	69·8 ± 3·5*
20	92·2 ± 5·7	67·2 ± 3·5*
40	87·0 ± 10·6	57·7 ± 5·1*

* $P<0·05$

Stereotyped behaviour

Administration of apomorphine hydrochloride (0·5 mg kg^{-1} s.c. 15 min previously) or (+)-amphetamine sulphate (5 mg kg^{-1} i.p. 30 min previously) to rats induced stereotyped behaviour consisting of sporadic locomotion, continuous sniffing and discontinuous licking, gnawing or biting (Fig. 1). (−)-Sultopride produced a dose-dependent antagonism of both amphetamine- and apomorphine-induced stereotyped behaviour (ID50 7·3 and 10·5 mg kg^{-1} respectively). Total inhibition of stereotyped behaviour was apparent at 15 mg kg^{-1} (−)-sultopride in each case. Very high doses of (+)-sultopride antagonized amphetamine-induced stereotyped behaviour (ID50 94 mg kg^{-1}), but apomorphine-induced stereotyped behaviour was only slightly reduced by 128 mg kg^{-1}.

In contrast to the enantiomers of sultopride, those of sulpiride caused only slight antagonism of stereotyped behaviour induced by apomorphine or amphetamine. A dose of 128 mg kg^{-1} produced a small decrease in stereotyped behaviour, but this was similar for both enantiomers.

Striatal and mesolimbic dopamine HVA and DOPAC concentrations

Pretreatment of animals with (−)-sulpiride (2–100 mg kg^{-1} 3 h previously) elevated striatal and mesolimbic HVA and DOPAC concentrations (Fig. 2). No change in dopamine concentrations in either area was observed. Treatment with (+)-sulpiride (2–100 mg kg^{-1} i.p.) did not alter striatal or mesolimbic HVA, DOPAC or dopamine values.

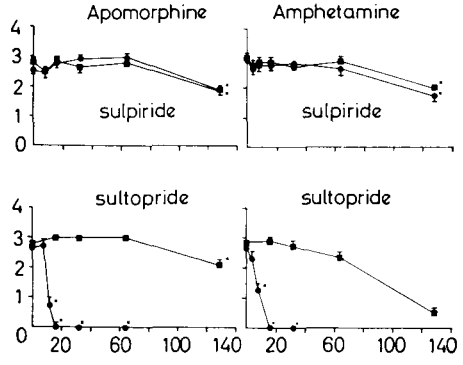

FIG. 1. The effect of (+)- or (—)-sultopride and (+)- or (—)-sulpiride on stereotyped behaviour in rats induced by administration of apomorphine hydrochloride (0·5 mg kg^{-1} s.c.) or (+)-amphetamine sulphate (5 mg kg^{-1}). Each result is the mean (±s.e.m.) for at least 8 rats at each dose level used. * $P < 0.05$ compared with saline-treated controls receiving apomorphine or amphetamine alone. Ordinate: stereotypy score. Abscissa: dose (mg kg^{-1}). ● (−)-isomers. ■ (+)-isomers.

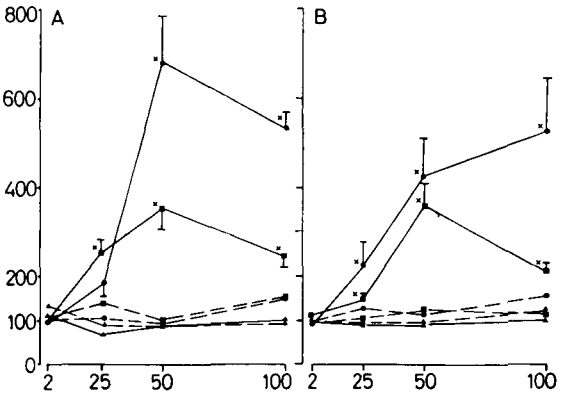

FIG. 2. Concentrations of HVA (●), DOPAC (■) and dopamine (▲) in the striatum (A) and mesolimbic (B) brain areas of rats pretreated with (+)- (– – –) or (−)- (——) sulpiride (2–100 mg kg^{-1} i.p.) 3 h before death. Each result is the mean (±s.e.m.) for at least 4 separate determinations at each dose level used. * $P < 0.05$ compared with saline-treated control mice. Ordinate: HVA, DOPAC or dopamine levels as % of control values. Abscissa: dose (mg kg^{-1}).

Administration of (−)-sultopride (2–50 mg kg^{-1} 1·5 h previously) also elevated striatal and mesolimbic HVA and DOPAC concentrations. Dopamine concentrations were slightly decreased at 25 and 50 mg kg^{-1}, but were unchanged at 2 mg kg^{-1} (Fig. 3). Pretreatment with (+)-sultopride did not alter striatal or mesolimbic HVA values, but at 25 and 50 mg kg^{-1} did elevate DOPAC in both areas. A small decrease in dopamine was again apparent following (+)-sultopride 25 and 50 mg kg^{-1} but only in the mesolimbic area.

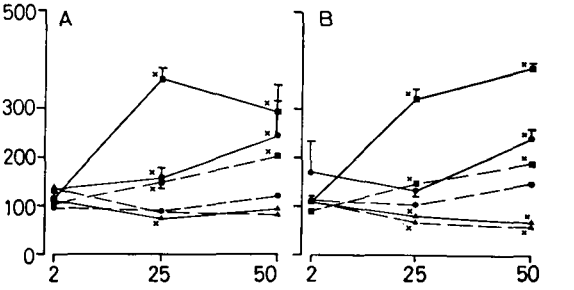

FIG. 3. Concentrations of HVA (●), DOPAC (■) and dopamine (▲) in the striatum (A) and mesolimbic (B) brain areas of rats pretreated with (+)- (– – –) or (−)- (——) sultopride (2–50 mg kg^{-1}) 1·5 h before death. Each result is the mean (±s.e.m.) for at least 4 separate determinations at each dose level used. * $P < 0.05$ compared with saline treated control animals. Axes as for Fig. 2.

Striatal dopamine sensitive adenylate cyclase

The addition of dopamine (10^{-4} M) to striatal homogenates produced an increase in cyclic (c)AMP formation (Table 2). Neither enantiomer of sulpiride or sultopride (10^{-8} – 10^{-4} M) antagonized this, the (−)-enantiomers of both drugs producing a small increase in cAMP formation although this did not appear to be concentration-dependent.

Specific [^{3}H]spiperone binding to striatal preparations

The specific binding of [^{3}H]spiperone to receptor sites was assessed by the stereoselective displacement of ligand by (+)-butaclamol (2×10^{-6} M) or (−)-butaclamol (2×10^{-7} M). Under these conditions total binding of [^{3}H]spiperone was between 11·5 – 15·5 pmol g^{-1} wet weight tissue, of which approximately 90% represented specific stereoselective binding. The ability of the enantiomers of sulpiride and sultopride to displace [^{3}H]spiperone was compared with this butaclamol-sensitive component to assess the extent of specific displacement and enantiomeric potency.

The incorporation of (−)-sulpiride (10^{-9} – 5×10^{-6} M) into incubates produced a concentration-dependent displacement of [^{3}H] spiperone binding (IC50 $3{\cdot}6 \times 10^{-7}$ M) (Fig. 4). (+)-Sulpiride only caused displacement at concentrations above 10^{-6} M (IC50 $>5 \times 10^{-6}$ M). An approximate 40-fold difference in potency between the enantiomers was apparent.

The incorporation of (−)-sultopride into the striatal preparation produced a concentration-dependent displacement of [^{3}H]spiperone binding (IC50 $6{\cdot}6 \times 10^{-4}$ M) (Fig. 4). (+)-Sultopride only caused displacement at concentrations in excess of 10^{-7} M (IC50 $>5 \times 10^{-6}$ M). An approximate 80-fold difference in potency between isomers was apparent

Neither (−)-sulpiride nor (−)-sultopride in the highest concentration (5×10^{-6} M) employed caused a maximal displacement of specific [^{3}H]spiperone binding when compared with the stereoselective displacement caused by butaclamol. In the presence of (−)-sulpiride and (−)-sultopride (5×10^{-6} M) 21·4 and 15·4% of the butaclamol-sensitive binding component remained undisplaced.

Table 2. The effect of (+)- or (−)-sulpiride (10^{-8} —10^{-4} M) or sultopride on dopamine (10^{-4} M)-stimulated adenylate cyclase activity in rat striatal preparations. For the sulpiride enantiomers basal cAMP levels were 31·4 pmol cAMP per 2 mg tissue wet weight per 2·5 min. Dopamine (10^{-4} M) increased this value to 56·1 pmol cAMP per 2 mg tissue wet weight per 2·5 min ($P < 0{\cdot}05$). For the sultopride enantiomers, studied on another occasion, basal levels were 65·7 pmol cAMP per 2 mg tissue wet weight per 2·5 min and dopamine stimulated levels 93·6 pmol cAMP per 2 mg tissue wet weight per 2·5 min ($P < 0{\cdot}05$). The differences between these values represent normal run to run variation for this procedure.

Addns to *incubates* M	cAMP formed per 2 mg tissue wet weight every 2·5 min as % of stimulation caused by dopamine (10^{-4} M) alone			
Dopamine 10^{-4}	100·0 ± 2·1 Sulpiride enantiomers		100·0 ± 2·4 Sultopride enantiomers	
	(+)-	(−)-	(+)-	(−)-
$+10^{-8}$	97·3 ±2·7	102·7 ±3·4	100·0 ±4·1	122·1 ±4·3*
$+10^{-7}$	92·0 ±1·8*	119·3 +1·4*	109·5 ±4·3	113·2 ±2·6*
$+10^{-6}$	102·9 ±3·2	114·1 ±5·9*	103·6 ±2·1	124·5 ±2·1*
$+10^{-5}$	100·0 ±3·2	113·4 ±5·5*	103·3 ±1·8	109·5 ±2·6*
$+10^{-4}$	102·7 ±1·8	124·1 ±2·0*	111·6 ±2·7*	123·2 ±4·0*

* $P < 0{\cdot}05$

DISCUSSION

The neuropharmacological profile of substituted benzamide drugs suggests an action on both pre- and post-synaptic cerebral dopamine receptors. Thus

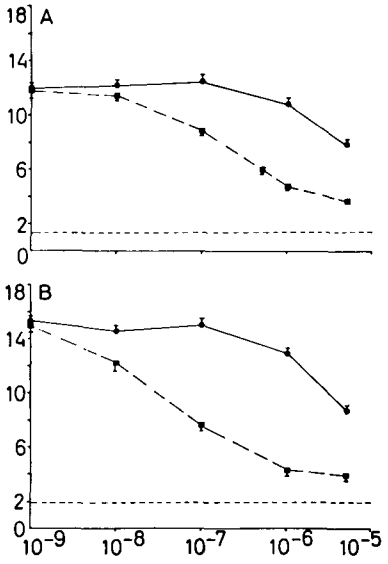

FIG. 4. Displacement of total [^{3}H]spiperone (0·5 nM) binding to rat striatal preparations by (A) (+)- (●) or (—)- (■) sulpiride or (B) (+)- (●) or (—)- (■) sultopride (10^{-9} —5×10^{-6} M). The extent of the stereoselective displacement of [^{3}H]spiperone produced when (+)-butaclamol (2×10^{-6} M) is incorporated into incubates is indicated by the dashed line. Ordinate: total binding of [^{3}H]spiperone (pmol g^{-1} wet weight time). Abscissa: concentration (M).

these compounds prevent both the sedation caused by administration of low doses of apomorphine (believed to preferentially affect presynaptic receptors) (Di Chiara et al 1976) and the excitatory responses produced by higher doses of apomorphine (which activate post-synaptic receptors) (Elliott et al 1977). However, substituted benzamides do not produce marked catalepsy (Laville 1972; Costall & Naylor 1975; Elliott et al 1977) or inhibit dopamine-stimulated adenylate cyclase (Trabucchi et al 1975; Jenner et al 1978a,b) which has led to the hypothesis that such compounds act specifically on one subpopulation of cerebral dopamine receptors (Jenner et al 1978a; Kebabian 1978; Kebabian & Calne 1979).

Apomorphine-induced locomotor activity was antagonized by (−)-sulpiride and (−)-sultopride but not by the (+)-isomers. However, in each case less than 50% of total activity was abolished in the dose-range used, the dose-response curves being shallow and showing little dependence on the dose. That the benzamide enantiomers only partially inhibited apomorphine-induced locomotion may reflect their action on a limited population of those dopamine receptors responsible for the initiation and control of locomotion. Lesion experiments with kainic acid suggest that adenylate cyclase-linked dopamine receptors lie post-synaptically on those neurons on which dopamine neurons synapse, at least in striatum (Schwarcz et al 1978). A reasonable conclusion is that benzamide drugs only partially antagonize apomorphine-induced locomotion because they do not block those post-synaptic cyclase-linked dopamine receptors.

The effect of benzamide drugs on apomorphine locomotion was stereoselective, and a stereoselective action of (−)-sultopride compared with its (+)-enantiomer also was evident in the antagonism of apomorphine- and amphetamine-induced stereotyped behaviour. However, neither sulpiride enantiomer nor the racemate antagonized this drug-induced stereotyped response (Puech et al 1976; Jenner et al 1978a,b). The reason for this is not known but the observation illustrates differences between the actions of individual benzamide drugs at dopamine receptor sites within the brain. Sulpiride penetrates the brain poorly (Hondo et al 1977; Costall et al 1978) but this is unlikely to be responsible for the lack of activity against stereotyped behaviour. Thus (−)-sulpiride (in doses ineffective against stereotypy) elevated striatal and mesolimbic HVA and DOPAC concentrations while the (+)-enantiomer was inactive in altering dopamine turnover confirming the stereoselective action of the (−)-isomer observed in some behavioural experiments. The (−)-enantiomer of sultopride overall, was also more effective than the (−)-enantiomer in altering dopamine turnover, but the latter did elevate striatal and mesolimbic DOPAC concentrations.

The effects on specific [^{3}H]spiperone binding to striatal receptors also illustrated the greater activity of the (−)-enantiomers of sultopride and sulpiride. The (—)-isomers at high concentrations caused some displacement, but this was an effect seen with most isomeric drugs tested (for example (+)- and (−)-butaclamol; *cis* and *trans*-flupenthixol) (Burt et al 1976) and may, to some extent be dependent on the enantiomeric purity of the compounds.

The failure of the highest concentrations of (−)-sulpiride and (−)-sultopride to produce a maximal displacement of [^{3}H]spiperone (as judged using (+)-butaclamol) is in agreement with other data for racemic sulpiride (Briley 1978). Although [^{3}H]-spiperone also labels cerebral 5-hydroxytryptamine (5-HT) receptors, this does not appear to occur in striatal preparations (Leysen et al 1978b). Further, the specific binding of [^{3}H]spiperone in striatal preparations resistant to displacement by racemic sulpiride is not displaced by 5-HT antagonists (Briley 1978) but may indicate the existence of a population of dopamine receptors at which drugs such as sulpiride and sultopride are ineffective.

The present findings are in agreement with previous studies on (+)- and (−)-sulpiride. Thus, (−)-sulpiride has been shown to preferentially displace [^{3}H]haloperidol from its striatal binding site (Garau et al 1978) and to antagonize ADTN-induced hyperactivity following bilateral injection into nucleus accumbens (Andrews & Woodruff 1978). Further, its stereoselective action in elevating DOPAC concentrations in striatal and mesolimbic areas of rat brain has been recorded (Hofmann et al 1979).

Despite the specificity of behavioural and biochemical action of the (−)-isomers of sulpiride and sultopride so far described, they did not antagonize dopamine stimulation of striatal adenylate cyclase activity which supports previous findings suggesting that such compounds do not act on receptors dependent on adenylate cyclase (Trabucchi et al 1975; Roufogalis et al 1976; Jenner et al 1978a,b). Indeed, the (−)-isomers of optically active benzamides such as sultopride and sulpiride may be of considerable use in the study of non-cyclase dependent cerebral dopamine receptors. The small increase in dopamine stimulation of adenylate cyclase activity that appeared to be caused by (−)-sulpiride

and (−)-sultopride could represent a compensatory change in cyclase-dependent systems as a result of an antagonist action of these drugs at cyclase-independent dopamine receptors.

The stereoselectivity of benzamide enantiomers observed in brain does differ from that observed in studies of peripheral dopamine receptors. Thus, the isomers of sulpiride exert different effects on the 'pre-' and 'post-synaptic' sites associated with renal vascular dopamine receptors (Goldberg et al 1979). The ability of dopamine to cause renal vasodilation by action at a specific vascular receptor (post-synaptic response) is preferentially inhibited by (+)-sulpiride. However, the ability of dopamine to inhibit the release transmitter from the post-ganglionic sympathetic nerve by action on a neuronal receptor (pre-synaptic response) is preferentially inhibited by (−)-sulpiride. It would appear from these data that the peripheral presynaptic receptor rather than the peripheral post-synaptic site resembles the central adenylate cyclase-independent dopamine receptor. Also, the observation that (+)-sulpiride failed to induce or inhibit cerebral dopamine function suggests the post-synaptic vascular receptor would not appear identical to the equivalent cerebral site.

In conclusion we have shown that the central actions of optically active benzamide drugs, such as sulpiride and sultopride, are due mainly to the (−)-enantiomers which appear to act on a cyclase-independent receptor population, but the different effects of sultopride and sulpiride on stereotyped behaviour suggests that this may not necessarily be a single entity.

Acknowledgements

This study was supported by the Wellcome Trust and the Research Funds of King's College Hospital and the Bethlem Royal and Maudsley Hospitals. We thank SESIF, France Ltd. and Ayerst Laboratories for generous supplies of compounds.

REFERENCES

Andrews, C., Woodruff, G. N. (1978) Br. J. Pharmacol. 64: 434P

Briley, M. S. (1978) at Symposium on Receptors of Dopamine Antagonists New Biochemical Approaches Beerse, Belgium

Burt, D. R., Creese, I., Snyder, S. H. (1976) Mol. Pharmacol. 12: 800–812

Costall, B., Naylor, R. J. (1975) Psychopharmacologia (Berlin) 43: 69–74

Costall, B., Fortune, D. H., Naylor, R. J. (1978) J. Pharm. Pharmacol. 30: 796–798

Di Chiara, G., Porceddu, M. L., Vargiu, L., Argiolas, A., Gessa, G. L. (1976) Nature (London) 264: 564–567

Elliott, P. N. C., Jenner, P., Huizing, G., Marsden, C. D., Miller, R. (1977) Neuropharmacology 16: 333–342

Garau, L., Govono, S., Stefanini, E., Trabucchi, M., Spano, P. F. (1978) Life. Sci. 23: 1745–1750

Goldberg, L. I., Kohli, J. D., Listinsky, J. J., McDermed, J. D. (1979) Proc. 4th Int. Catecholamine Symposium, in the press

Hofmann, M., Jommi, G. C., Montefusco, O., Tonon, G. C., Spano, P. F. Trabucchi, M. (1979) J. Neurochem. 32: 1547–1550

Hondo, F., Satoh, V., Shimomura, K., Satoh, H., Noguchi, H., Uchida, S., Kato, R. (1977) Jpn. J. Pharmacol. 27: 397–411

Iversen, L. L., Rogawski, M. A. Miller R. J. (1976) Mol. Pharmacol. 12: 251–262

Jenner, P., Clow, A., Reavill, C., Theodorou, A., Marsden, C. D. (1978a) Life. Sci. 23: 545–550

Jenner, P., Eliott. P. N. C., Clow, A., Reavill, C., Marsden, C. D. (1978b) J. Pharm. Pharmacol. 30: 46–48

Kebabian, J. W. (1978) Life. Sci. 23: 479–484

Kebabian, J. W., Calne, D. B. (1979) Nature (London) 277: 93–96

Laville, Cl. (1972) Lille Med. Actual. 17: Suppl. 4–13

Leysen, J., Gommeren W., Laduron, P. M. (1978a) Biochem. Pharmacol. 27: 307–316

Leysen, J. E., Niemegeers, C. J. E., Tollenaere, J. P., Laduron, P. M. (1978b) Nature (London) 272: 168–171

Miller, R. J., Horn, A. S., Iversen, L. L. (1974) Mol. Pharmacol. 10: 759–765

Puech, A. J., Simon, P., Boissier, J-R. (1976) Eur. J. Pharmacol. 36: 439–441

Roufogalis, B. D., Thornton, M., Wade, D. N. (1976) Life. Sci. 19: 927–934

Schwarcz, R., Creese, I., Coyle, J. T., Snyder, S. H. (1978) Nature (London) 271: 766–768

Trabucchi, M., Longoni, R., Fresia, P., Spano, P. F. (1975) Life. Sci. 17: 1551–1556

Westerink, B. H. C., Korf, J. (1977) J. Neurochem. 29: 697–706